

### **REMARKS**

Claims 1-16 and 18-27 are pending. Claims 13 and 15 are under examination. In this response, claim 13 has been amended. Support for the amendment can be found throughout the specification and, for example, on page 23, lines 7-8. Claim 15 has been canceled without prejudice. No new matter has been added. Entry, reexamination and reconsideration in light of the preceding amendments and following remarks are respectfully requested.

Applicant submits that the above amendments place the application in condition for allowance, as they address the Office's rejections of the claims, or in the alternative place the claims in better form for a subsequent appeal. Applicant therefore respectfully request that the amendments be entered, and the amended claims be allowed.

#### **I. CLAIM REJECTION UNDER 35 U.S.C. § 102(E)**

Claims 13 and 15 stand rejected under 35 U.S.C. §102(e) as being anticipated by Newmark et al. (U.S. Patent No. 6,391,346 at col. 1, lines 14-17, col. 3, lines 55-60, col. 4, lines 30-end, col. 6, lines 25-35; hereinafter "Newmark") or Babish et al. (U.S. Patent Publication No. 2003/0008021 at paragraphs 25, 33, 34; hereinafter "Babish").

Despite the Applicant's previous showings that iso-alpha acids are not generated during supercritical-CO<sub>2</sub> hop extraction, the Office maintains that Babish suggests that such compounds are generated because Babish lists isohumulone as one of the compounds present in the  $\alpha$ -acid fraction of CO<sub>2</sub> hop extract in paragraph 34. The Office also maintains that Newmark's CO<sub>2</sub> hop extracts are inclusive of iso-alpha acids in view of the teachings of Babish and French abstract, FR 2590589 (which, as Applicant pointed out previously, is directed to a process for the photoisomerization of alpha acids to iso-alpha acids during the supercritical CO<sub>2</sub> extraction process and does not teach or suggest that iso-alpha acids can generate on their own during the CO<sub>2</sub> extraction process). Office Action, pages 3-5.

The Office further maintains that “[t]he COX-2/COX-1 ratio is inherent to the composition of hops since iso alpha acids are also what applicant uses in their application to treat mammals. The extraction is done exactly as applicant’s (using supercritical CO<sub>2</sub>) thus the same ratio is inherently produced.” Office Action, page 4, paragraph 2. Applicant respectfully traverses the rejection for the reasons of record and the following reasons.

In view of the amended claim 13, Applicant avers that contrary to what the Office contends, the extraction process in Babish and Newmark is not done exactly as Applicant’s, and thus it cannot be presumed that the same COX-2/COX-1 ratio is produced. Applicant has stated in the application as filed that the alpha acids in hops extract are isomerized by heating the high viscosity extract with potassium hydroxide and another mineral salt in aqueous solution. See the application as filed on page 8, lines 13-15 and Example 7 on page 23, lines 7-8. Neither Babish nor Newmark (nor FR 2590589) refers to a step of heating with potassium hydroxide in their CO<sub>2</sub> extraction processes.

As such, Applicant respectfully submits that the specific IC50-WHMA COX-2/COX-1 ratio of about 0.23 to about 3.33 recited in claim 13 is novel over the teachings of Babish and Newmark and not inherent to the composition of hops, even if, *arguendo*, isoalpha acids are obtained during the supercritical CO<sub>2</sub> extraction process.

Also, in paragraph [0086], Babish asserts that CO<sub>2</sub> extract of hops showed a COX-1/COX-2 specificity of 106. If the ratio is inverted to be comparable with the ratio of the present application, a COX-1/COX-2 ratio of 106 equals a COX-2/COX-1 ratio of  $1/106 = 0.0094$ , which is far smaller than the ratio range of 0.23-3.33 presently claimed. This evidence further shows that a COX-2/COX-1 ratio of about 0.23 to about 3.33 is not inherent to the composition of hops obtained using supercritical CO<sub>2</sub>.

According to MPEP § 2131, “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior

art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

In view of the claimed COX-2/COX-1 ratio being neither expressly nor inherently described in either of Babish or Newmark, Applicant avers that claim 13 does not read on Babish or Newmark and is not anticipated by them. Accordingly, Applicant respectfully requests withdrawal of this rejection.

## **II. CLAIM REJECTION UNDER 35 U.S.C. § 103(A)**

Claims 13 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Newmark et al. (U.S. Patent No. 6,391,346 at col. 1, lines 14-17, col. 3, lines 55-60, col. 4, lines 30-end, col. 6, lines 25-35; hereinafter “Newmark”) or Babish et al. (U.S. Patent Publication No. 2003/0008021 at paragraphs 25, 33, 34; hereinafter “Babish”).

As stated above, despite the Applicant’s previous showings that iso-alpha acids are not generated during supercritical-CO<sub>2</sub> hop extraction, the Office maintains that such compounds are generated in view of the teachings of Babish and French abstract, FR 2590589.

The Office further states on page 7 of the Office Action that “[t]he COX-2/COX-1 ratio is inherent to the composition of hops since iso alpha acids are also what applicant uses in their application to treat mammals. The extraction is done exactly as applicant’s (using supercritical CO<sub>2</sub>) thus the same ratio is inherently produced.” The Office continues in paragraph 3, on page 7 of the Office Action that “in the event that the ratio of claim 13 is not inherent to the composition...then it would have been at least obvious to one having ordinary skill in the art to purify the hops extract to such a ratio in an effort to optimize the desired result.” Applicant respectfully disagrees for the reasons of record and the following reasons.

As mentioned above in response to the 102 rejection and in view of amended claim 13, in contrast to what the Office contends, the extraction process in Babish and Newmark

is not done exactly as Applicant's, and thus it cannot produce the same COX-2/COX-1 ratio. Applicant has stated in the application as filed that the alpha acids in hops extract are isomerized by heating the high viscosity extract with potassium hydroxide and another mineral salt in aqueous solution. See the application as filed on page 8, lines 13-15 and Example 7 on page 23, lines 7-8. Neither Babish nor Newmark (nor FR 2590589) refers to a step of heating with potassium hydroxide in their CO<sub>2</sub> extraction processes.

As such, Applicant respectfully submits that the specific IC50-WHMA COX-2/COX-1 ratio of about 0.23 to about 3.33 recited in claim 13 is novel over the teachings of Babish and Newmark and not inherent to the composition of hops, even if, *arguendo*, isoalpha acids are obtained during the supercritical CO<sub>2</sub> extraction process.

Applicant further avers that the present claims are drawn from the new and unexpected results that neither Babish nor Newmark taught or suggested. Applicant has unexpectedly discovered that COX-2 inhibitors having an IC50-WHMA COX-2/COX-1 ratio of about 0.23 to about 3.33 would be selective enough to inhibit COX-2 over COX-1, but not so selective that they would result in the additional cardiovascular and gastrointestinal side effects. See the application as filed on page 3, line 19 to page 4, line 5; and page 5, line 28 to page 6, line 3.

In the Background section, Applicant describes why too much COX-2 over COX-1 selectivity may not be desirable. For example, rofecoxib and celecoxib (specific COX-2 inhibitors) were shown to cause cardiovascular side effects when taken alone or cause worsening of gastric erosion when taken with aspirin (a specific COX-1 inhibitor). See the application as filed on page 3, lines 19-24.

As such, Applicant avers that the specific IC50-WHMA COX-2/COX-1 ratio of 0.23-3.33 was discovered unexpectedly to be effective without undesirable side effects in the treatment method claimed, and the ratio is not inherent to the composition of hops for the reasons discussed above, even if, *arguendo*, isoalpha acids are obtained during supercritical CO<sub>2</sub> extraction process.

Applicant also disagrees with the Office's suggestion that one having ordinary skill in the art at the time the present application could have arrived at the claimed ratio through routine optimization work "within purview of the skilled artisan. Office Action, page 7, paragraph 4.

Applicant further submits that Babish not only fails to teach or suggest a COX-2/COX-1 ratio of 0.23-3.33 but also teaches away a skilled artisan from arriving at the claimed COX-2/COX-1 ratio of 0.23-3.33. As mentioned above, in paragraph [0086], Babish asserts that CO<sub>2</sub> extract of hops showed a COX-1/COX-2 specificity of 106. If the ratio is inverted to be comparable with the ratio of the present application, a COX-1/COX-2 ratio of 106 equals a COX-2/COX-1 ratio of  $1/106 = 0.0094$ , which is far smaller than the ratio range of 0.23-3.33 presently claimed. Babish attributes such a high COX-2 specificity, as compared to pure humulone, to "underlying synergy among the bioactive molecules." See Babish, paragraph 86.

In Babish, emphasis is on utilizing the above synergy and achieving a high COX-2 specificity—corresponding to a low COX-2/COX-1 ratio—by using two or more active ingredients from hops. This goal of achieving a maximal COX-2 specificity ("2.7 fold greater than the COX-2 specificity demonstrated for pure humulone" Babish, paragraph 86, lines 7-8) or minimal COX-2/COX-1 ratio is implicitly emphasized throughout the Babish reference in, for example, the abstract, paragraph 25 and claim. A skilled artisan familiar with Babish's work would have been led away from contemplating or wishing to obtain a COX-2/COX-1 ratio of about 0.23 to about 3.33 which is considered to be too high representing a very low COX-2 selectivity when compared to Babish's teachings.

With respect to Newmark, Applicant respectfully maintains, for the reasons of record, that Newmark only concerns supercritical CO<sub>2</sub> extract of hops. Even if, *arguendo*, the compositions of Newmark could contain isoalpha acids (when combined with FR 2590589 and/or Babish), as discussed above, Newmark still fails to inherently or explicitly teach or suggest the element of COX-2/COX-1 ratio of 0.23-3.33 presently claimed in

amended claim 13. As taught by Babish, a CO<sub>2</sub> extract of hops have a COX-2/COX-1 ratio of 0.0094. There is nothing in Newmark that could motivate a skilled artisan to make a bioavailable composition of iso-alpha acids, isomerized through heating the high viscosity extract with potassium hydroxide, with a specific COX-2/COX-1 ratio of about 0.23-3.33 to arrive at the method presently claimed.

Newmark further teaches a skilled artisan away from contemplating the specific ratio of COX-2/COX-1 of about 0.23-3.3 when Newmark states: '[w]ith respect to the extracts of melissa, valerian, hops and chamomile, the term "therapeutically effective amount" means that amount of the herb which will promote sleep without interfering with the composition's anti-inflammatory properties.' See Newmark, column 4, lines 49-53. A skilled artisan familiar with Newmark's work would have been led to focus more on promoting sleep than optimizing the COX-2/COX-1 ratio.

In view of the KSR decision and based on the new MPEP § 2143 guidelines for establishing *prima facie* case of obviousness, combining references should be based on a rationale supported by a clear articulation of the reason(s) why the claimed invention would have been obvious. In particular, the Supreme Court in KSR notes that "[w]hen the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." *KSR*, 82 USPQ2d at 1395 1395-97 (2007).

Accordingly, Applicant respectfully submits that Newmark *et al.*, and/or Babish *et al.*, even if combined with FR 2590589 still fails to render the instant invention *prima facie* obvious. It is, therefore, respectfully submitted that, for the reasons of record and above reasons, the amended claim 13 is patentable over Newmark and/or Babish when considered individually or in combination with FR 2590589. As such, Applicant respectfully requests withdrawal of this rejection.

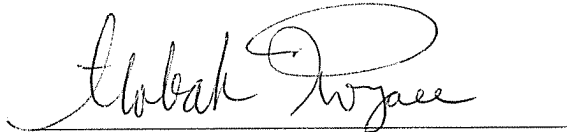
**III. CONCLUSION**

In light of the remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned agent at the telephone number provided below.

To the extend necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to deposit account 50-1133 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in cursive script, reading "Atabak Royace", written over a horizontal line.

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